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INDIAN TRADITIONAL THERAPIES AND BIO-PROSPECTING: THEIR ROLE IN DRUG DEVELOPMENT RESEARCH

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ABSTRACT: Exploration of biological diversity for identification of novel bioactive molecules or therapeutically more potential than the marketed products is a continuous ongoing process for drug development research. Indian traditional therapies have been a part of our lifestyle since ages. Due to their knowing ability and applications, this knowledge has long been used as thriving sources for discovery of new drug molecules. Historical text or traditional knowledge including folklore, ethnobotany or ethnopharmacological studies are proving to be a powerful tool for searching lead molecules for the development of new drugs. This review article presents the contribution on 33 medicinal plants along with their traditional uses, bioactive constituents, biological activities, chemical structures, and 30 marketed drug formulations at national and international markets. A brief note on the recent discovery on osteogenic compounds from *Ulmus wallichiana,* folk traditional plant used for healing fractured bones in Uttarakhand Himalaya is also discussed in this article.

INTRODUCTION: Medicinal properties of plant species have made an outstanding contribution in the origin and evaluation of many traditional therapies. These traditional knowledge systems have started to disappear with the passage of time, due to lack of scientific investigations.

Over the past few years, however, the medicinal plants (10-18 % of total medicinal plant biodiversity) have regained a wide recognition and estimate revealed that 70-80% population of the world rely on herbal products due to its lesser side effects as compared to allopathic medicines.

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Indian sub-continent is well known for its diversity and several ethnic groups (more than 84.4 million people) mainly Gonds, Santhal, Khasis, Angmis, Bhutias, great Andmanese etc with age-old culture, traditions, languages, lifestyle and healthcare systems [1]. Most of them are still untouched with rest of the world. For their health care system they rely only on their own traditional medicines.

Ethnobotany is also one of the emerging areas in drug development research and ethnobotanical driven discovery of novel pharmacological agents [2, 3, 4] also highlights the potential for using collected indigenous knowledge as a research tool. The loss of relevant information of traditional knowledge and medicinal properties of number of plant species is inestimable, but it is likely to be significant from pharmacological perspective, because more than half of the current chemotherapeutic cancer drugs and > 100 marketed pharmaceutical have been derived from plant sources [4, 5].

Prostratin, an HIV therapeutic that activates the latently infected T-cell pool a potentially beneficial and lucrative compound identified through ethnobotanical work in Samoa [2]. Medicinal properties of plants were known even to pre-historic men and many of these plants have been used in traditional medicine for hundreds of years with reputation as efficacious remedies [6, 7].

Large numbers about 297000 native species worldwide, 52885 (10%) species are reported as medicine [8]. As per Indian scenario, out of 17,000 species of higher plants, 7500 species (44%) are known as medicinal [9]. Primitive human societies have been depending on plants and plant products for various remedies. Ayurveda, the oldest medical system in Indian sub-continent has alone reported 2000 plants followed by 1300 in Siddha, 1000 Unani, 500 Tibetan and 800 in Homeopathy [10].

However, a major percentage more than 4500 plant species are used in folk traditions for the treatment of different ailments (**Table 1**). As per the world scenario, China is the biggest country with 11,146 species followed by 1600 species in North-West Amazonia [11, 12, 13]. A significant percentage in developed countries like Belgium (31%), USA (42%), Australia (48%), France (49%), Canada (70%) are also rely in traditional and alternative remedies for their health care [14]. World market for herbal remedies and number of plant species used in Indian traditional medicines are presented in **Table 1 & 2**.

Evidences and status of bioprospecting the Indian traditional knowledge: The current scenario of ongoing demand of medicinal plant and their pharmaceutical products have several reasons, including faith in herbal products, affordable price and less side effects as compared to the allopathic medicines. Approximately 25 % of drugs are derived from plants of which 33 marketed formulations at national market (i.e. bronchodilator, piles, memory enhancer, constipation, anti-amoebic, anti-fertility and fertility enhancer, immunomodulators, respiratory diseases, tonics, antiulcer, skin diseases, diuretic, aphrodisiac, antidiabetic/lipid lowering, antioxidants, antiobesity, digestive & carminative, anti-inflammatory, hepatoprotective, anti-bacterial/anti-fungal, gynecological) and 30 formulations at global market were derived from Indian traditional plants (**Tables 3 & 4**) [15, 16, 17].

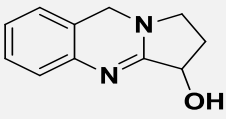
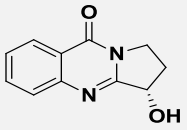
TABLE 1: NUMBER OF PLANTS USED IN DIFFERENT INDIAN TRADITIONAL SYSTEMS OF MEDICINES

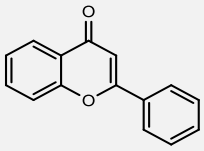
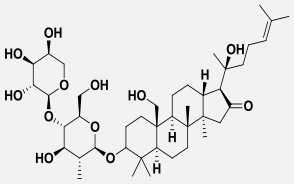
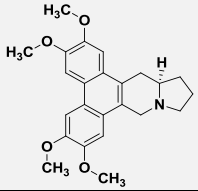
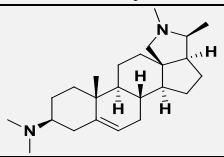
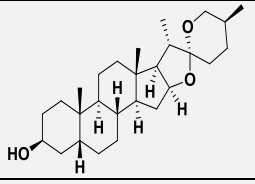
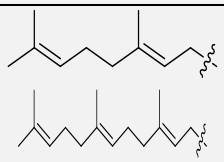
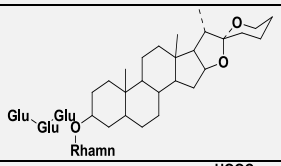
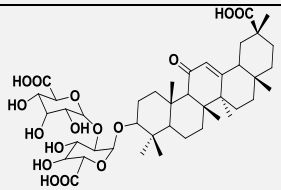
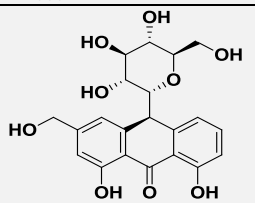
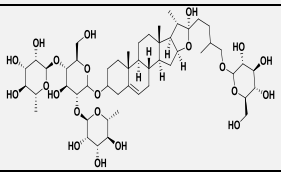
Traditional medicinal system	No. plant species used
Folk-tradition	4500
Ayurveda	2000
Siddha	1300
Unani	1000
Homeopathy	800
Tibetan	500
Modern	200

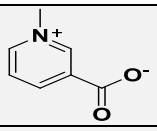
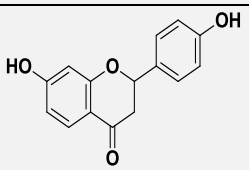
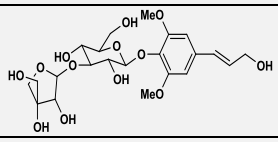
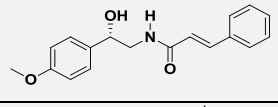
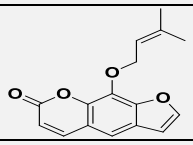
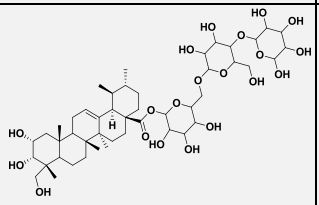
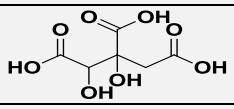
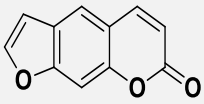
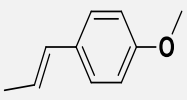
TABLE 2: WORLD MARKETS OF HERBAL REMEDIES

Continent/zone/country	Percentage
Europe	33
North America	20
Asia	26
Japan	11
Others	10

TABLE 3: EVIDENCES OF BIO-PROSPECTING OF DRUG MOLECULES DERIVED FROM INDIAN TRADITIONAL PLANTS

Plant	Traditional uses	Bioactive Compound	Structure of bioactive compounds	Biological activity	Marketed/ traditional formulations
Adhatoda vasica Nees	Asthma, rheumatism, cough, chronic bronchitis,	Vasicine, vasicinone	 	Bronchodilator	Diakof®, Koflet®

Euphorbia prostrata Aiton	Piles	Flavonoids		Piles	Thank god®
Bacopa monnieri L.	Nerve tonic, Asthma, Snake bite	Baccosoids		Memory enhancer	Mentat®, Himalayan bramhi®
Cassia sp.		Sennosides	-	Constipation	Kayamchurna®
Tylophora indica Burm.f.	Ipecacuanha, Emetic	Tylophorine		Bronchodilator	Fizzle®,Vassafort e®
Holarrhena antidysentrica Wall.	Fever, Dysentry, Diarrhea	Conessine		Antiamoebic	Kutajarista
Asparagus adscendens Roxb.	Treatment of impotency	Sarsasapoge-nin, asparanin A and asparanin B		Fertility enhancer	Spermon®
Ocimum sanctum L.	Cold & cough, bronchtis, Snake bite	Monoterpen-es, sesquiterpenes		Immunomodulat ory & respiratory diseases	Kofostal®, syrup,Curill® capsule
Asparagus racemosus Willd.	Treatment of impotence	Shatavarin		Tonic, galactogogue	Geriforti®
Glycyrrhiza glabra L.	Cough, Genito-urinary diseases, Scorpion-sting	Glycrrhizin		antiulcer, anti-tussive	Kofex®
Aloe vera Tourn. ex L.	Skin disorders	Aloin		Demulcent, skin diseases	Clarina®
Tribulus terrestris L.	Impotence, kidney diseases, Painful micturition, Urinary discharges	Protodiosin		Diuretic, aphrodisiac, anabolic	Gokshura

Trigonella foenum-graecum L.	Cooling drink,Tonic Dysentry	Trigonellin		Antidiabetic, lipid lowering	Ayuslim®
Withania somnifera (L.) Dunal	Adaptogenic	Withanolides	-	Immunomodulatory	Ashwagandharista
Embelia ribes Burm.f.	Fever, disease of chest and skin, Ascariasis, Cough, diarrhea	Natural product	-	Antifertility	Pipalayadi yoga
Pterocarpus marsupium Roxb.	Astrin, Pyrosis, Skin disorders	Liquiritigenin,isoliquiritigenin		Antidiabetic	Diabecon
Tinospora cordifolia (Willd.)Hook. J. & Thomson	Aphrodis, Nutrient, Chronic diarrhea dysentry.	Tinosporic acid, Cordifoliosides		Immunomodulatory	Himalaya Guduchi®
Aegle marmelos Corr.	Astrin, Intermittent fever, Fish poison, stomach disorders	Aegelin, marmelosin	 	Bowel disease	Diarex®
Phyllanthus emblica L.	One of the ingredient of *Trifla*	Polyphenolics, tannins	-	Antioxidant	Chyavanprash
Centella asiatica L.	Leprosy, Memory enhancer, Certain type of Tuberculosis	Asiaticoside		Memory enhancer	Mentat®
Garcinia cambogia Desr.	-	Hydroxycitric acid		Antiobesity	Ayuslim®,Bioslim®
Areca catechu L.	Aphrodis, Urinary disorders, Nerve tonic, Anthelmic	Tannins	-	Antiobesity, anti-tussive	koflet®,Bioslim®
*Psoralea corylifolia*L.	Leprosy, Deobstruent, Leucoderma	Psoralen		Vitiligo	Pigmento®
Gmelina arborea L.	Cough, Foetid discharges, Ulcers	Natural product	-	Tonic, stomachic	Chyavanprasha
Achyranthes aspera L.	Piles, Skin diseases, Astrin	Achyrenthin	-	Diuretic	Cyston®
Anethum graveolens L.	-	Anethole		Digestive, carminative	Bonnisan®
Argyreia nervosa (Burm.f.) Bojer	-	Alkaloids	-	Aphrodisiac, fertility enhancer	Confide®

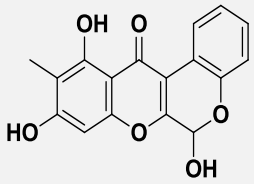
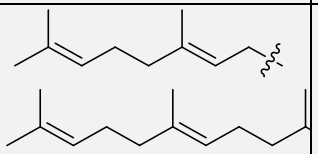
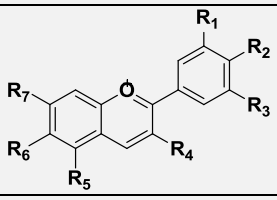
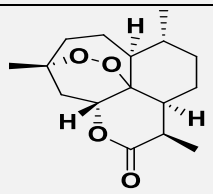
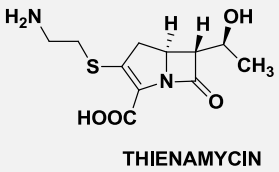
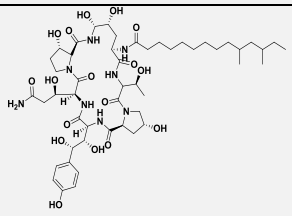
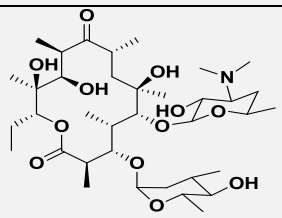
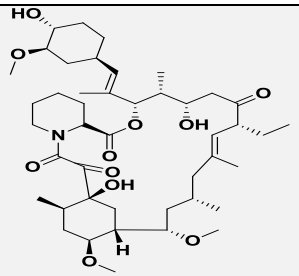
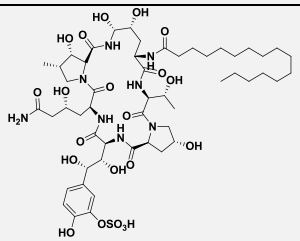
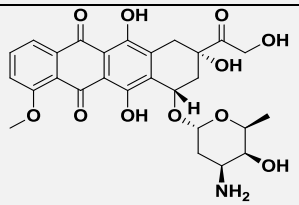
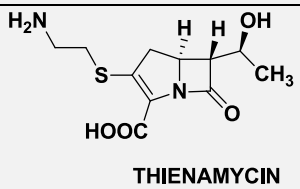
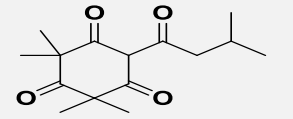
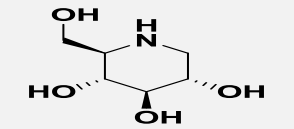
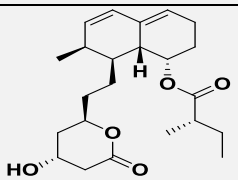
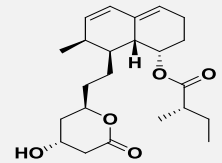
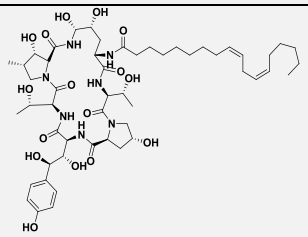
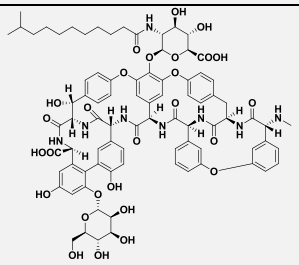
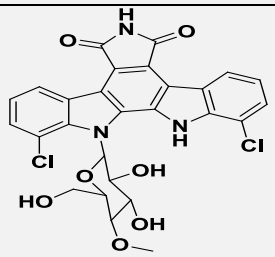
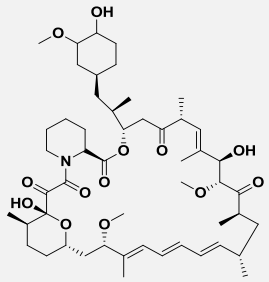
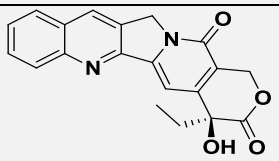
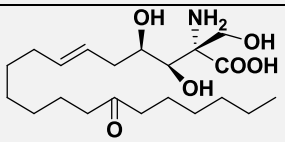
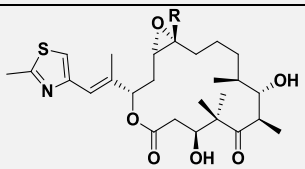
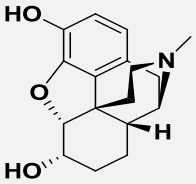
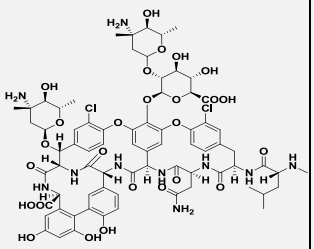
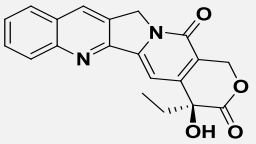
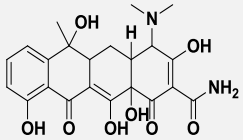
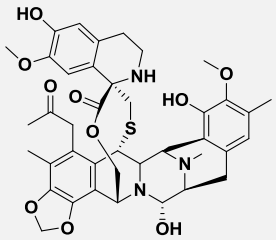
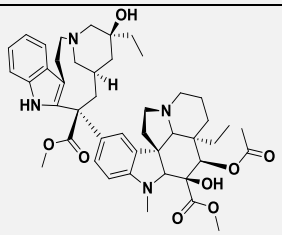
Vitex negundo L.	Headache, Acute rheumatism, Fever, Removing foetid discharges	Flavonoids	-	Anti-inflammatory	himcolin®
Boerrhavia diffusa L.	Asthma, Oedema, Anaemia, Jaundice	Boeravinones		Hepatoprotective	Live 52®
Cyperus rotundus L.	Astrin. Stomach disorders, Bowels irritation	Monoterpenes & Sesquiterpenes		Antibacterial, antipyretic	Himpyrin®
Eugenia jambolana L.	-	Anthocyanins		Antidiabetic	Diabecon®
Evolvulus alsinoides L.	Asthma,chr.bronchitis,tonic	Flavonoids	-	Tonic, bitter	Anxocare®
Symplocos recemosa Roxb.	Astrin, Eye diseases, Ulcers,	Alkaloids	-	Gynaecological disorders	Evecare®

TABLE 4: GLOBAL SCENARIO OF MARKETED NATURAL PRODUCTS OR NATURAL PRODUCT DERIVED DRUGS [13]

Name of drug	Lead compounds	Chemical structures	Original sources	Disease	Company (originator)
Arteether (Artemotil)	Artemisinin		*Artemisia annua* (Plant)	Anti-malarial	Artecef BV
Ertapenem (Invanz)	Thienamycin	 THIENAMYCIN	*Streptomyces cattleya (Fungi)*	Antibacterial	Merck (AstraZeneca)
Caspofungin (Cancidas)	Pneumocandin B		*Glarea lozoyensis (Fungi)*	Antifungal	Merck (Merck)
Telithromycin (Ketek)	Erythromycin		*Saccharopolyspora erythraea* Synonym *Streptomyces erythreus* (Fungi)	Antibacterial	Aventis (Aventis)

Pimecrolimus (Elidel)	Ascomycin		*Streptomyces hygroscopicus* var. *Ascomyceticus* (Fungi)	Atopic dermatitis	Novartis (Novartis)
Galantamine (Reminyl)	Natural product	-	*Galanthus* spp. later from *Narcissus* spp. (Plant)	Alzheimer's disease	Johnson & Johnson (Trad. Med. From Eastern Europe)
Micafungin (Funguard)	FR901379		*Coleophoma empetri* (Fungi)	Antifungal	Fujisawa (Fujisawa)
Amrubicin hydrochloride (Calsed)	Doxorubicin		*Streptomyces peucetius* (Fungi)	Anticancer	Sumitomo (Sumitomo)
Biapenem (Omegacin)	Thienamycin	 THIENAMYCIN	*Streptomyces cattleya* (Fungi)	Antibacterial	Meiji Seika (Wyeth)
Nitisinone (Orfadin)	Leptospermone	 LEPTOSPERMONE	*Callistemon citrinus (Plant)*	Antityrosinaemia	Rare Diseases Therapeutics (AstraZeneca)
Miglustat (Zavesca)	1-deoxynojirimycin		*Streptomyces trehalosaticus* (Fungi & Plants)	Type 1 Gaucher disease	Actelion/Teva (CellTech)
Mycophenolae sodium (Myfortic)	Natural product	-	*Penicillium brevicompactum* (Fungi)	Immunosuppressi on	Novartis*c*
Rosuvastatin (Crestor)	Mevastatin		*Penicillium citrimun* and *P. brevicompactum* (Fungi)	Dyslipidemia	AstraZeneca (Shionogi & Co)
Pitavastatin (Livalo)	Mevastatin		*Penicillium citrimun* and *P. brevicompactum* (Fungi)	Dyslipidemia	Sankyo/Kowa (Kowa/Nissan Chemical)

Daptomycin (Cubicin)	Natural product	-	*Streptomyces roseosporus* (Fungi)		Antibacterial
Anidulafungin (LY-303366)	Echinocandin B		Originally *Aspergillus rugulovalvus* Syn *Aspergillus rugulosus* (Fungi)	Antifungal	Vicuron Pharmaceutical
Dalbavancin (BI-397)	A40926 antibiotic		Isolated from *Nonomuraea* sp. (Actinomycete)	Antibacterial	Vicuron Pharmaceutical
Edotecarin	Rebeccamycin		Isolated from *Saccharothrix aerocolonigenes* (Actinomycete)	Anticancer	Pfizer and Banyu
Everolimus	Sirolimus (Rapamycin)		*Streptomyces hygroscopicus* (Fungi)	Immune-suppression	Novartis
Exatecan	Camptothecin		*Camptotheca acuminate* (Plant)	Anticancer	Daiichi Pharmaceuticals
FTY720	Myriocin		*Mycelia sterilia* and *Myriococcum albomyces* (Fungi)	Immunosuppres-sion	Novartis
Ixabepilone	Epothilone B		*Sorangium cellulosum* (Bacteria)	Anticancer	Bristol-Myers Squibb

M6G (morphine-6-glucuronide)	Morphine		*Papaver somniferum* (Plant)	Pain	CeNeS
Oritavancin	Chloroeremoy-cin (LY264826)		*Nocardia orietalis/ amycolatopsis orientalis* (Actinomycete) (Fungi)	Antibiotic	InterMune
Ramoplanin (INN) complex	-	-	*Actinoplanes* sp. ATCC 33076 (Actinomycete)	Antibiotic	Oscient Pharmaceuticals
Rubitecan (Orathecin)	Camptothecin		*Camptotheca acuminate* (Plant)	Anticancer	SuperGen
Tigecycline (Tygacil)	Tetracycline		*Streptomyces Aureofaciens* (Fungi)	Antibiotic	Wyeth
Trabectedin(ET-743, Yondel	Trabectedin		*Ecteinascidia turbinata* (Mangrove tunicate)	Anticancer	PharmaMar/ Johnson & Johnson
Ziconotide	ö-conotoxin MVIIA	-	*Conus magus* (Gastropod mollusk)	Chronic pain	Elan
Vinflunine	Vinblastine		*Catharanthus roseus* (Plant)	Anticancer	Pierre Fabre

Bio-prospecting of medicinal plant diversity can also contribute sustainable management of traditional knowledge and natural resources, poverty reduction, and economic development and can provide;

(a) Bioactive chemical compounds libraries for high throughput screening (HTS).

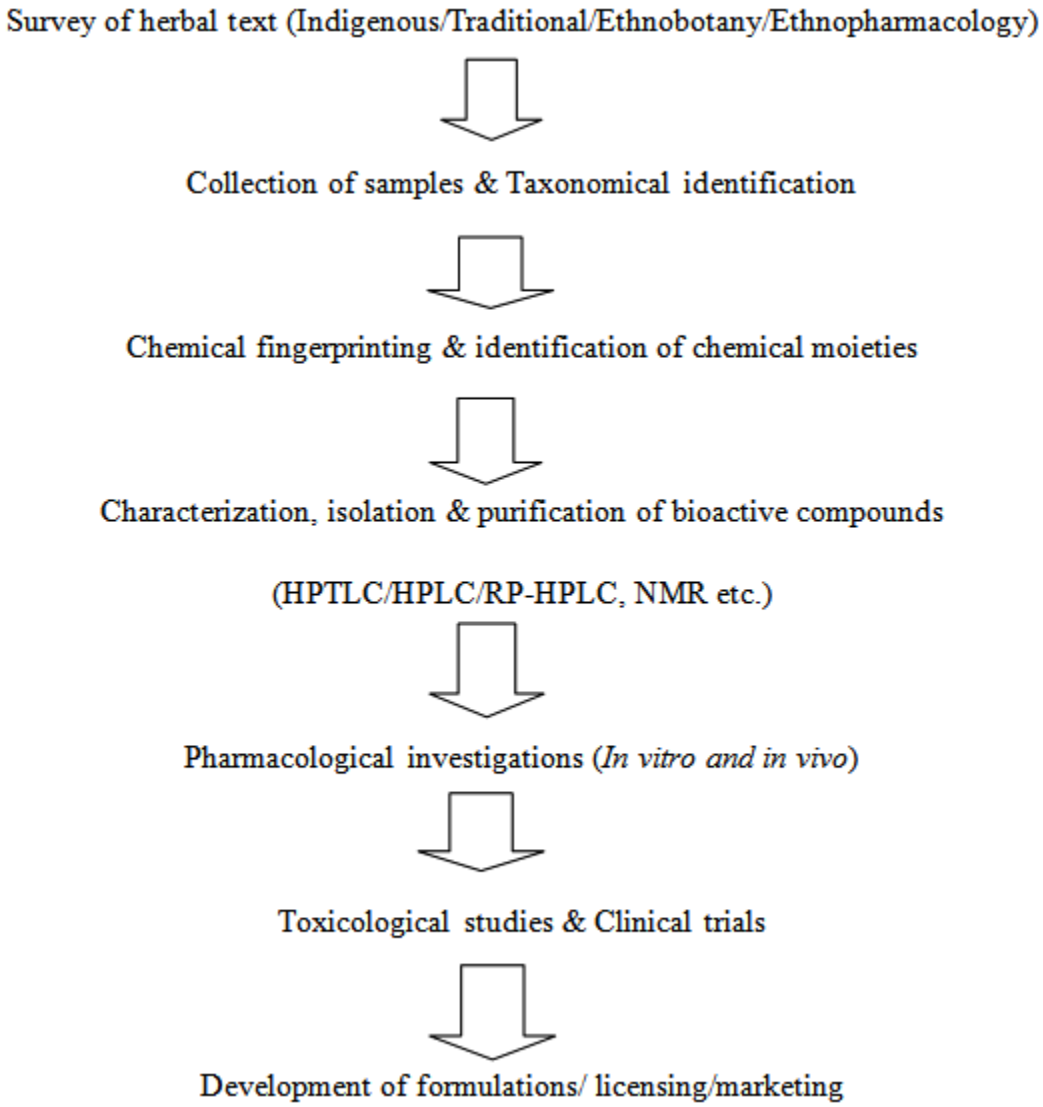
(b) Generate more alternative ways of treatment.

(c) Validates traditional knowledge and may provide naturally occurring novel bioactive leads with lesser side effects.

(d) Generate new alternatives of revenues from intellectual outputs with monetary benefits

such as farming, forestry, grazing, and fisheries, along with foods, medicines, fibers, and industrial development i.e. bioremediation, ecological restoration, and biomimetics etc.

Methodology for bio-prospecting of natural resources using traditional knowledge:



Recent discovery on naturally occurring osteogenic compounds from *Ulmus wallichiana* Planchon- a folk traditional plant used for healing fractured bones: Many natural agents known in traditional medicine have the potential to treat bone diseases; however, not much laboratory work has been reported evaluating their possible development and use. As a matter of fact, there is a resurgence of research on naturally-derived agents for potential anti-osteoporosis therapy. There are about 300 million people in India with osteoporosis [18]. Although the incidence of osteoporosis is alarmingly high in India, lack of awareness about the disease delays diagnosis and preventive measures. This is true even at the government level. Whereas in U.S., NIH alone spends ~$600 million (Rs 2700 crore)/year for osteoporosis research for her 44 million people suffering from this disease, no data on India's spending on this silent epidemic is available. Recent data indicate that Indians have much lower bone density than their North American and European counterparts, and that osteoporotic fractures occur 10-20 years earlier in Indians as compared to Caucasians [19-20]. As regards the burden of osteoporosis in the Indian scenario, 50% women have osteoporosis and in actual numbers it accounts for 200 million women, as there are more women than men at any elderly age group [18].

Hence, putting a check on osteoporosis has become a research area of considerable national importance. Bone formation by osteoblast involves several steps like proliferation of pre-osteoblast and their recruitment by chemotaxis to site of eventual bone formation, followed by their differentiation to mature, bone forming osteoblast that ultimately give rise to mineralized matrix. The ability to mineralize is the most desirable and ultimate point in osteoblast biology.

Therefore, any putative bone anabolic agent must have the ability to promote mineralization. Thus, it is essential to study whether extracts/fractions/pure compounds enhance mineralized matrix formation. It is said that osteoporosis is a 'silent epidemic' and a huge problem in India [18]. Lately, the problem of osteoporosis is being increasingly noticed. Therapeutic options of osteoporosis are limited to anti-resorptive drugs with limited efficacy in restoring bone health following bone loss. Bone forming (osteogenic/anabolic) therapy is limited to only parathyroid hormone (PTH). In addition to being extremely costly, PTH is not widely available in India. Therefore, finding bone anabolic agent is an unmet medical need. Herbal medicines are in great demand in the developed as well as developing countries for primary healthcare because of their wide biological activities, higher safety margins and lesser costs.

Recently, under drug development programme of CSIR-Central Drug Research Institute (CDRI), Lucknow has identified *Ulmus wallichiana*, a folk traditional plant used for healing fractured bones in animals as well as in human beings in folk tradition of Kumaon and Garhwal Himalaya, Uttarankhand [21].

Plant species is endemic to Western Himalaya and under endangered category [22, 23, 24] and grows about the elevation of 1800M to 3000M. As the plant is under endangered category, all the conservation measures during collection of bark samples had been followed [25, 26].

Bark of this plant is crushed to make fine paste and boiled. Semi solid and cooled paste is applied around the fractured parts and tightened with a thin cloth with giving a gentle support with cardboard and then the patient is allowed for rest for a period of 20 to 30 days depending upon the problems.

On the basis of this information, bark samples of this plant was collected from Uttarakhand Himalaya and investigated.

During investigations, we have been isolated four pure compounds K058, K012, K068, K100 (Figure-1) rich in C-glycosylated flavonoid and (2S,3S)-aromadendrin-6-C-β-D glucopyranoside is a novel flavonol [27, 28, 29] and has been licensed to Kemxtree, USA as rapid bone fracture healing anabolic agents for product development. Pharmacologically, these compounds showed peak bone mass achievement and prevention of menopausal bone loss in growing rats and stimulate osteoblast function and inhibit osteoclast and adipocyte differentiation in overiectamized rat [29, 30].

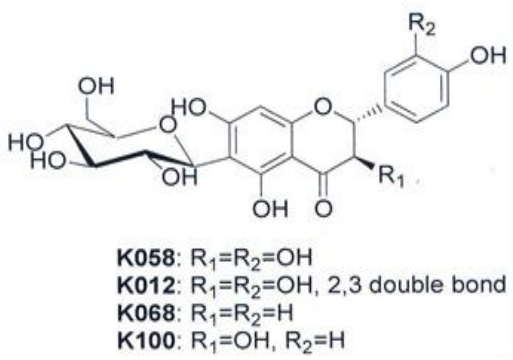


FIG. 1: CHEMICAL STRUCTURE OF BIOACTIVE COMPOUNDS FOR OSTEOGENIC ACTIVITY ISOLATED FROM STEM BARK OF *ULMUS WALLICHIANA* PLANCHON

Bone anabolic therapy- a treatment of rebuilding new bone is an unmet need. The only available bone anabolic agent today is a fragment of human parathyroid hormone (PTH) that suffers from limitations like prohibitive cost of treatment, safety aspects including bone cancer, daily administration by injection making treatment less favourable, and could only be given to a patient once in a life for maximum period of 2 years. These isolated molecules from the stem bark of this plant species claim to overcome many of these disadvantages associated with PTH.

CONCLUSION: Historical herbal texts as a resource in drug discovery became an important tool for Bio-prospecting the biological diversity of the country and provided new ways for further R&D to investigate detail phytochemical constituents and their pharmacological activities, which may lead to the discovery of novel bioactive molecules.

The systematic analysis of overall trends exhibited researchers to redirect their efforts towards different taxonomical groups or geographic regions, in order to improve the efficiency of their studies and maximize the number of new natural products (NPs) being discovered. There is also need to develop and screen a large number of pure compound and plant extract libraries to make the most out of what is available.

These approaches can surely be a driven force for the drug discovery from Indian traditional plants and lead to fruitful results for mankind. Despite of significant development of rural health services, a great deal of traditional knowledge of the use of medicinal plants for the treatment of several common ailments like cough, cold, fever, constipation burns cuts, scalds, boils, ulcers, skin diseases, respiratory troubles, joints pain, bone fractures and several neurological disorders are still intact with the rural and tribal practitioners.

Majority of them are required their proper documentation and scientific investigations. However, the traditional uses of lesser-known medicinal plants are disappearing rapidly and creating threat for extinction not only the plants, but also several naturally occurring bioactive compounds also. There is an urgent need to make a bridge between scientists, academics and the rural traditional practitioners to documents all the traditional information on plants for identification/ modification for the existing hits to get better lead compounds from natural resources.

Competing Interests: The authors declare that they have no competing interest.

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